REMARKS

Prior to this Amendment, claims 1-27 were pending. By this Amendment, claims 11-16 and 22-27 have been canceled in response to the Restriction Requirement. The Applicants reserve the right to prosecute the canceled claims in continuing applications.

Amendments to the specification

The amendments to the specification have been made because the figures were inadvertently incorrectly described in the "Brief Description of the Figures" section. This would have been obvious to one skilled in the art and it would have been obvious how to correct the "Brief Description of the Figures" section.

It is clear that Figure 4 is an FTIR spectrum because inspection of Figure 4 reveals the characteristic plethora of peaks, with typical cm^{-1} values, of an FTIR spectrum. Further, page 4, lines 14-17, of the specification lists the peaks in the FTIR spectrum of Form VI. The peaks listed match those shown in Figure 4. Accordingly, the "Brief Description" of Figure 4 has been amended to reflect that Figure 4 is an FTIR spectrum of Form VI. To be consistent with the amended "Brief Description," the specification, at page 4, lines 14-17, has been amended to recite "FIG. 4" rather than "FIG. 2."

Since the original "Brief Description" of Figure 2 as an FTIR spectrum was incorrect, Figure 2 must actually be one of the other two spectra described in the application, i.e., either a DSC thermogram or a DTG thermogram. Inspection of the text within Figure 2 indicates that it reads "Method: DSC." Accordingly, the "Brief Description" of Figure 2 has been amended to reflect that Figure 2 is a DSC thermogram of Form VI. The specification, at page 4, lines 18-20, has been amended to recite "FIG. 2" rather than "FIG. 3" in order to be consistent with the amendment to the "Brief Description" of Figure 2.

That leaves Figure 3 as the DTG thermogram of Form VI. The "Brief Description" of Figure 3 and the specification, at page 4, lines 21-24, have been amended to reflect this.

Claim objections

Claims 2-10 and 17 were objected to as being substantial duplicates of claim 1.

While all of claims 1-10 and 17 are directed to Form VI, the scope of coverage of Form VI varies according to the limitations recited in each claim in that the scope of coverage

is determined by the limitations recited in a claim and each of claims 1-10 and 17 recites different limitations for Form VI. Accordingly, different proofs would be required for each of claims 1-10 and 17 in order to determine if a particular crystalline form falls within the scope of those claims.

M.P.E.P. §706.03(k) states that "mere difference in scope between claims has been held to be enough" to prevent claims from being considered substantial duplicates. Here all of claims 2-10 and 17 differ in scope from claim 1 because it is necessary to satisfy different limitations to fall within the scope of claim 1 on the one hand and claims 2-10 and 17 on the other. Claim 1 is directed to a crystalline form of carvedilol that can be characterized by any of: (1) a PXRD pattern with certain peaks, (2) a DSC thermogram with certain endothermic peaks, or (3) an FTIR spectrum with certain peaks. Thus, to fall within the scope of claim 1, it is only necessary that the crystalline form be characterized by any of (1)-(3).

In contrast, to fall within the scope of claims 2-10 and 17, it is necessary to show that a crystalline form have at least one characteristic that it is not necessary to show for claim 1. For example, to fall within the scope of claim 2, the crystalline form must be shown to have the PXRD peaks recited in claim 2. To fall within the scope of claim 3, the crystalline form must be shown to have the PXRD peaks recited in claim 2 as well as the PXRD peaks recited in claim 3. Similarly, claims 4-10 and 17 recite characteristics that the crystalline form must be shown to have to fall within the scope of claims 4-10 and 17 but that it is not necessary for the crystalline form to be shown to have to fall within the scope of claim 1.

This alone provides for a difference in scope between claim 1 and each of claims 2-10 and 17 and leads to the conclusion that an objection of claims 2-10 and 17 as being substantial duplicates of claim 1 is improper.

Court decisions have upheld an applicant's right to claim an invention in a reasonable number of ways. *See In re Flint*, 411 F.2d 1353, 1357 (C.C.P.A. 1969) ("applicants should be allowed reasonable latitude in stating their claims in regard to number and phraseology employed."); *In re Chandler*, 319 F.2d 211, 225 ("[t]he right of applicants to freedom of choice in selecting phraseology which truly points out and defines their inventions should not be abridged.").

In view of the above, it is respectfully requested that this objection be withdrawn.

The rejections under 35 U.S.C. §112

Claims 18-21 were rejected for lack of enablement.

This rejection relies on two premises: (1) metabstable crystalline forms tend to convert to the most stable form; and (2) the usual procedures used to prepare pharmaceutical compositions (grinding, milling, adding excipients, etc.) will convert a metastable form to a stable form.

The Applicants traverse this rejection because the evidence cited to support the first premise is insufficient and no evidence supporting the second premise has been cited.

The only evidence cited in support of this rejection is Rouhi, Chemical and Engineering News, February 24, 2003, pages 32-35 (Rouhi).[1] Rouhi at most shows that metastable forms tend to, i.e., may possibly, convert to the most thermodynamically stable form. See the Office Action, page 4, lines 8-9: "Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32)."

The specification teaches that the claimed carvedilol Form VI can be formulated into pharmaceutical compositions. See page 6, line 1, to page 9, line 29. Thus, the specification teaches that Form VI will persist after being formulated into pharmaceutical compositions. The burden is on the Office Action to provide evidence or reasoning, not just mere speculation, as to why this teaching of the specification is incorrect. See *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971), where the United States Court of Customs and Patent Appeals stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein .... [emphasis in original]

439 F.2d at 223, 169 U.S.P.Q. at 369.

[1] Rouhi was cited in the PTO-892 Form accompanying this Office Action.

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. [italics in original; underscoring added]

439 F.2d at 224, 169 U.S.P.Q. at 370.

The Office Action has not met this burden. A premise of this rejection is that Form VI will not persist upon being formulated into a pharmaceutical composition. This goes far beyond the evidence that the Office Action has cited in support of this rejection. The cited evidence (Rouhi) at most shows that metastable forms may possibly convert to the most thermodynamically stable form. The cited evidence says nothing about the likelihood, the speed of, or the completeness of, such a conversion.

There is nothing in Rouhi that supports the proposition that Form VI is likely to convert so rapidly and so completely into the most stable form when formulated into a pharmaceutical composition that a person skilled in the art could not practice the invention defined in claims 18-21. Nor was any other evidence provided to support such a proposition.

The only reason given in the Office Action for such a proposition is the speculation that if Form VI is subjected to the usual procedures for making pharmaceutical compositions it will convert to other forms. See, e.g., the Office Action, page 4, lines 4-8:

> [T]he preparation of pharmaceutical compositions requires milling, adding excipients, surfactants, etc. The process of preparing a pharmaceutical composition, such as milling, will cause a specific crystalline from, if in the metastable state to resort back to the most thermodynamically stable form which is the form with the lowest vapor pressure. [underscoring added]

The key portion of the above passage is the underlined quote. This quote expresses the second premise underlying this rejection. The Office Action provided no evidence in support of this premise.

Furthermore, Rouhi teaches that the second premise underlying this rejection is wrong. Rouhi teaches that the likely outcome of formulation of a crystalline form, when

carried out by those skilled in the art, is that the crystalline form would maintain itself for a reasonable period of time such that the pharmaceutical composition would be useful. This is part of the teachings of Rouhi since one of the main themes in Rouhi is that pharmaceutical companies are actively seeking new crystalline forms of compounds (even metastable forms) in order to formulate these new crystalline forms into pharmaceutical compositions (see page 32, right column; "[M]uch effort is being expended looking for metastable forms of currently marketed drugs whose stable forms have been around for a long time." It would make no sense for pharmaceutical companies to behave in such a manner if the second premise underlying this rejection were correct.

Furthermore, conversion to the most stable form can be quite slow and less stable crystalline forms can co-exist with the most stable crystalline form. See U.S. Pharmacopia #23, National Formulary #18 (1995), page 1843, entry (941), X-Ray Diffraction[2]:

> Many compounds are capable of crystallizing in more than one type of crystal lattice. At any particular temperature and pressure, only one crystalline form (polymorph) is thermodynamically stable. Since the rate of phase transformation of a metastable polymorph to the stable one can be quite slow, it is not uncommon to find several polymorphs of crystalline pharmaceutical compounds existing under normal handling conditions.

The quotation above shows that the second premise underlying this rejection ignores the fact that, even if conversion to a more stable form occurs, conversion may be "quite slow." In fact, this quotation implies that such "quite slow" conversion is "not uncommon." Thus, the evidence of record indicates that the likely outcome of formulating Form VI into pharmaceutical compositions is that Form VI will persist, at least for a period of time sufficient to provide a useful pharmaceutical composition.

In view of the above, it can be seen that the evidence provided in the Office Action is inadequate to support this rejection. Thus, the Office Action failed to provide "acceptable evidence or reasoning" to support the rejection, as required by *Marzocchi*.

The Office Action reads claims 18-21 as including solutions of Form VI where the pharmaceutically acceptable carrier is water. See the Office Action, page 4, lines 10-13. The Applicants note that claim 18 is directed to a pharmaceutical composition comprising

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[2] This reference was cited in the PTO-892 Form accompanying this Office Action.

"the crystalline solid of carvedilol" of claim 1 (underscoring added). Claims 19-21 depend from claim 18 and thus also require solid carvedilol Form VI. In view of this, it is respectfully requested that this aspect of the rejection is in error.

The Applicants believe that the above discussion demonstrates that claims 18-21 do not lack enablement. In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 4 and 6-9 were rejected as being indefinite because of the referral to figures in claims 4, 6, and 9. It was suggested that the data from the figures be inserted into the claims.

Claims 4, 6, and 9 have been amended as suggested. Claim 4 has been amended to incorporate the data from Figure 1; claim 6 has been amended to incorporate the data from Figure 2; claim 9 has been amended to incorporate the data from Figure 4.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1, 2, 5-10, and 17-21 were rejected as being indefinite.

According to the Office Action, the claims must recite at least 10 PXRD peaks in order to be definite. Support for this position is supposedly found in Polymorphism in Pharmaceutical Solids, Brittain, ed., Marcel Dekker, New York, 1999, pages 1, 2, 178, 179, 185, 219, and 236 (Brittain).

The Applicants respectfully traverse this rejection. The portion of Brittain quoted in the Office action is concerned with what is necessary to establish the identity of two crystalline forms, i.e., whether a given crystalline form is identical to a reference crystalline form. This can be seen by examining both the quoted portion of Brittain and U.S. Pharmacopia #23, National Formulary #18 (1995), page 1843, entry (941), X-Ray Diffraction, which Brittain refers to. Brittain, at page 236, stated:

> The USP general chapter on x-ray diffraction states that identity is established if the scattering angles of the ten strongest reflections obtained for an analyte

> agree to within ±0.2 degrees with that of the reference material ...
> [underscoring added]
>
> U.S. Pharmacopia #23, at page 1844, stated:
>
> Agreement between sample and reference should be within the calibrated precision of the difractometer for diffraction angle (2θ values typically should be reproducible to ±0.10 or 0.20 degrees), while relative intensities between sample and reference may vary up to 20 percent. ... It is generally sufficient to scan past the ten strongest reflections identified in the Powder Diffraction File. [underscoring added]

In view of this, the quoted material is not relevant to the issue of the definiteness of the present claims. There is no requirement under 35 U.S.C. §112, paragraph 2, that the claims be drafted in such a manner that the recited characteristics of a claimed crystalline form allow one to establish that the claimed crystalline form is identical to a reference crystalline form. All that 35 U.S.C. §112, paragraph 2 requires in this context is that the claims "particularly point out" the claimed crystalline forms, i.e., distinguish the claimed crystalline forms from other crystalline forms. There is no set number of peaks that is necessary to do this. In fact, under the right circumstances, one peak might be sufficient.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986).

Claim 1 recites, in the alternative, 4 PXRD peaks, 2 DSC peaks, and 13 FTIR peaks. There is no doubt that one skilled in the art understands what a PXRD peak, a DSC peak, or an FTIR peak is and thus would understand the bounds of a claim that recites particular PXRD, DSC, or FTIR peaks. Such a claim simply covers subject matter that produces those peaks. For example, the bounds of claim 1, which recites 4 PXRD peaks, 2 DSC peaks, and 13 FTIR peaks, would be understood by one skilled in the art to encompass carvedilol crystalline Form VI that can be shown to produce those 4 PXRD peaks, 2 DSC peaks, or 13 FTIR peaks when analyzed in the appropriate manner.

Courts have expressed the test for definiteness in various ways. For example, the Federal Circuit, in *All Dental Prdx LLC v. Advantage Dental Products, Inc.*, 64 U.S.P.Q.2d

1945, 1949 (Fed. Cir., 2002) stated: "The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, e.g., competitors of the patent owner, can determine whether or not they infringe."

Claim 1 meets this test. For example, one skilled in the art could readily test a given carvedilol crystalline form to determine if it produced the 4 PXRD peaks, 2 DSC peaks, or 13 FTIR peaks that are recited in claim 1. In such a simple manner, it could thus be determined if the tested crystalline form infringes claim 1.

The same could be done for the additional characteristics recited in the other claims that were included in this rejection. Each of those claims recites a set of physical characteristics for which it would be a routine matter to test a potentially infringing carvedilol crystalline form, and thus determine whether that crystalline form infringes those claims.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1-10, and 17-21 were rejected as being indefinite. The Office Action stated that this rejection could be overcome by deleting the phrase "or a solvate thereof" from the claims.

The claims have been amended to delete the phrase "or a solvate thereof." Accordingly, it is respectfully requested that this rejection be withdrawn.

Claim 10 was rejected as being indefinite. Apparently, it is the lack of a recitation of PXRD, DSC, or FTIR data that prompted this rejection. See the Office Action, page 8, lines 10-14:

> Form VI is not a limiting element and does not define a difference in the carvedilol. Form VI is not a common well recognized term in the art to define anything. While Form VI is a term defined by the inventors, the definition is found in the instant specification as the PXRD, DSC thermogram and FTIR spectrum data. It is this data that distinguishes applicants' invention from the prior art and not the term Form VI.

The Applicants respectfully traverse this rejection. As explained above, the test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. The bounds of claim 10 would be understood in light of the specification. Even the quote above from the Office Action acknowledges this by stating that the definition of Form VI "is found in the instant specification as the PXRD, DSC thermogram and FTIR spectrum data." Given this definition in the specification, one of ordinary skill in the art could readily determine whether a crystalline form of carvedilol is Form VI simply by analyzing that crystalline form's PXRD, DSC, or FTIR spectrum to a sufficient degree to determine if it is Form VI.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §102(b)

Claims 1-10 and 17 were rejected as being anticipated by Chen et al., 1998, Chinese J. Struct. Chem. 17:325-328 (Chen).

The Applicants respectfully traverse this rejection. The IR peaks given by Chen at the top of page 326 indicate that Chen's crystalline form was not the same as Form VI. Chen's list of IR peaks includes peaks at 3346 cm^{-1} and 3087 cm^{-1} that are not present in the FTIR peaks of Form VI (see page 4, lines 14-17, for a list of FTIR peaks of Form VI). Exhibit C explains that IR readings and FTIR readings are comparable.

Claims 1-10 and 17-21 were rejected as being anticipated by U.S. Patent No. 4,503,067.

Example 2 of U.S. Patent No. 4,503,067 (col. 5, ll. 54-66) discloses a crystalline form of carvedilol having a melting point of 114°-115°C. International Patent Publication WO 99/05105,[3] at page 2, lines 28-29, discloses that Form II carvedilol has a melting point of 114°-115°C. Apparently, U.S. Patent No. 4,503,067 discloses Form II. Form VI is distinct from Form II, although Form VI can be transformed into Form II (see, e.g., the present specification, at page 3, line 30, to page 4, line 2). The transformation of Form VI into Form

[3] A copy of WO 99/05105 was included with the Information Disclosure Statement filed concurrently with the present application.

II can be seen in the DSC thermogram of Form VI shown in Figure 2 (reproduced in currently amended claim 6). The DSC thermogram of Form VI shows a strong peak at about 74°C, representing desolvation of Form VI. Continued heating beyond 74°C results in the transformation of Form VI into Form II. This is reflected in the small peak at about 114°C, representing the melting of Form II.

Since Form VI desolvated before giving rise to Form II, the crystal structure of Form VI must have a different solvent composition from Form II. Therefore, Form VI and Form II must be a different crystalline forms.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 1-10 and 17-19 were rejected as being anticipated by European Patent Application EP 0918055.

Examples 5-9 of EP 0918055 appear to disclose crystalline carvedilol. The crystalline carvedilol disclosed in these examples has a melting point that indicates that it is Form II. Thus, for the same reasons as are discussed above with respect to U.S. Patent No. 4,503,067, EP 0918055 does not disclose Form VI and does not anticipate the present claims.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 18-21 were rejected as being anticipated by European Patent Application EP 0893440.

EP 0893440 discloses Form I and Form II carvedilol. Form I and Form II are different crystalline forms as compared to Form VI because each of Form I, Form II, and Form VI have different PXRD patterns. The characteristic peaks of Form I and Form II are described at column 4, lines 51-55, of EP 0893440:

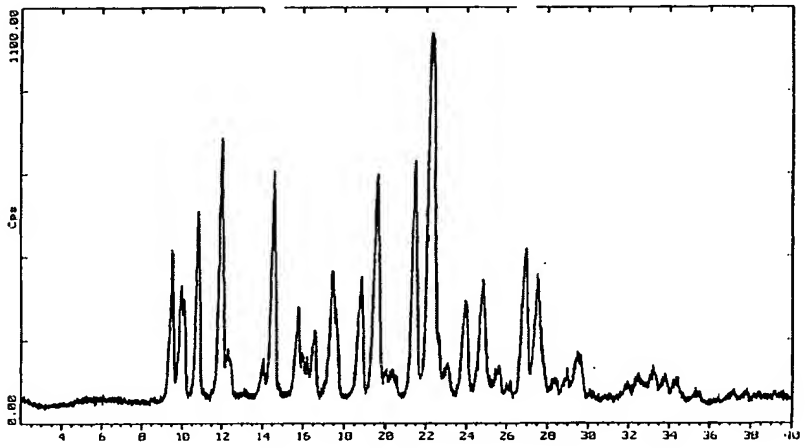
> The X-ray powder diffraction pattern of Form I has characteristic peaks occurring at 2θ = 9.5, 10.8, 12.0, 14.6, 19.6, 21.5, and 22.3 (Fig. 5) whereas the characteristic peaks of Form II occur at 2θ = 5.9, 14.9, 17.6, 18.5, and 24.4 (Fig. 6).

These PXRD peaks differ from the peaks that characterize Form VI. See the present application, at page 4, lines 10-13:

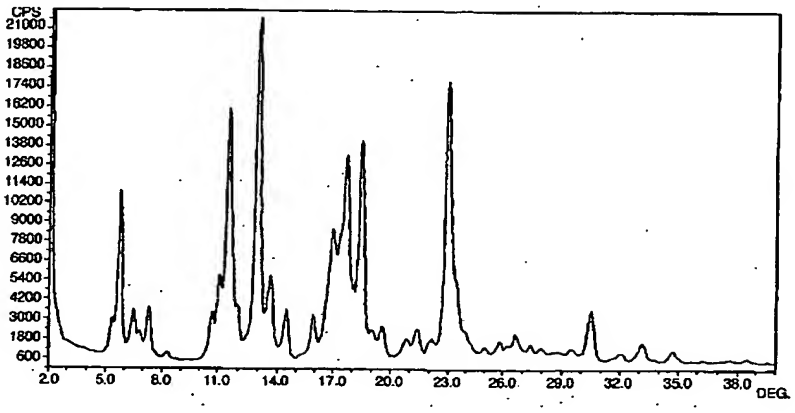
> Carvedilol solvate Form VI is characterized by a PXRD pattern (FIG. 1) with peaks at about 6.5, 7.3, 16.0, and 30.5±0.2 degrees two-theta. Further PXRD peaks were observed at about 5.8, 10.7, 11.1, 11.5, 13.1, 13.7, 16.8, 17.7, 18.5, and 23.0±0.2 degrees two-theta.

Furthermore, a comparison of the overall PXRD patterns of Forms I and II with that of Form VI indicates that Forms I and II are not the same as Form VI.

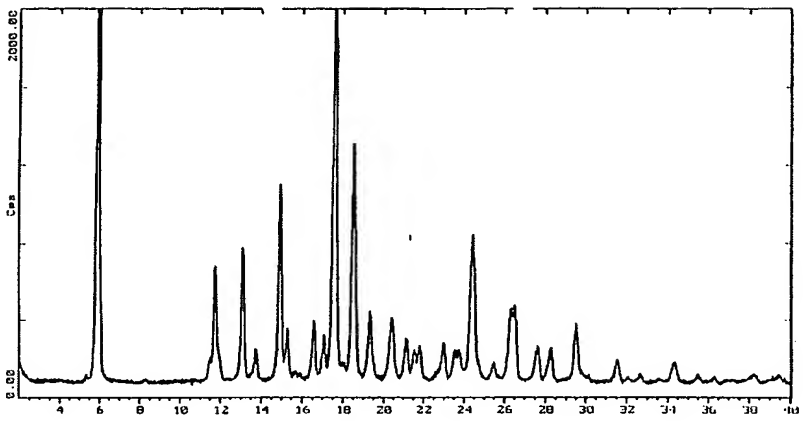
Form I (Figure 5 from EP 0893440)



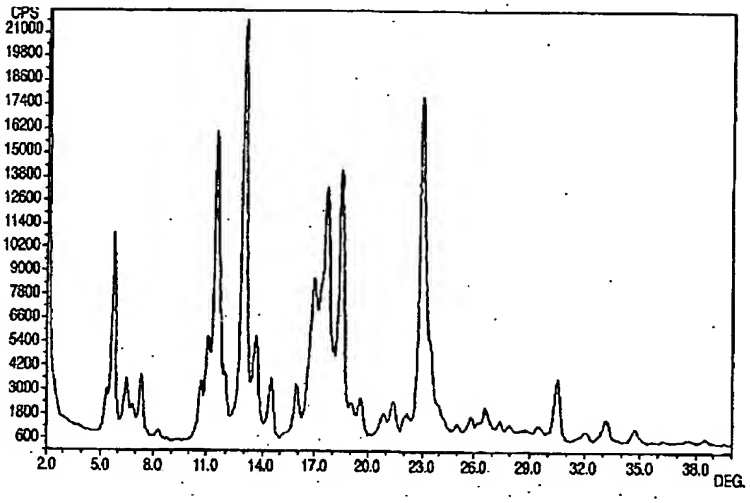
Form VI (Figure 1 of the present application)



Form II (Figure 6 from EP 0893440)



Form VI (Figure 1 of the present application)



Given these differences in PXRD patterns, it must be concluded that neither Form I nor Form II is the same crystalline form as Form VI.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 1-10 and 17-19 were rejected as being anticipated by International Patent Publication WO 99/05105.

WO 99/05105 appears to be the PCT publication corresponding to EP 0893440. Accordingly, it discloses the same Form I and Form II as EP 0893440. WO 99/05105

discloses the same characterizing PXRD peaks for Form I and Form II as EP 0893440 (see page 7, lines 8-10 of WO 99/05105). Thus, neither Form I nor Form II of WO 99/05105 is the same crystalline form as Form VI.

Accordingly, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §102(a) and (e)

Claims 18-21 were rejected as being anticipated under 35 U.S.C. §102(a) and (e) by International Patent Publication WO 02/00216.

WO 02/00216 discloses carvedilol Form III, Form IV, and Form V (a methyl-ethyl-ketone solvate). Forms III, IV, and V are different crystalline forms as compared to Form VI because each of Forms III, IV, and V has a different PXRD pattern from that of Form VI.

The characteristic peaks of Form III are described at page 15, lines 18-22, of WO 02/00216:

> Carvedilol Form III ("Form III") is characterized by an X-ray diffraction pattern with peaks at about 8.4 ± 0.2, 9.3 ± 0.2, 11.6 ± 0.2, 13.2 ± 0.2, 13.5 ± 0.2, 14.2 ± 0.2, 15.3 ± 0. 2, 15.8 ± 0.2, 17.4 ± 0.2, 18.4 ± 0.2, 19.4 ± 0.2, 20.6 ± 0.2, 21.4 ± 0.2, 22.0 ± 0.2, 26.5 ± 0.2 and 27.6 ± 0.2 degrees two-theta. The most characteristic peaks of Form III are at about 8.4 ± 0.2, 17.4 ± 0.2, and 22.0 ± 0.2 degrees two-theta.

The characteristic peaks of Form IV are described at page 16, lines 2-6, of WO 02/00216:

> Carvedilol Form IV ("Form IV") is characterized by an X-ray diffraction pattern with peaks at about 11.9 ± 0.2, 14.2 ± 0.2, 15.7 ± 0.2, 16.5 ± 0.2, 17.7 ± 0.2, 18.3 ± 0.2, 19.2 ± 0.2, 19.6 ± 0.2, 21.7 ± 0.2, 22.2 ± 0.2, 23.9 ± 0.2, 24.2 ± 0.2, 24.9 ± 0.2, 27.4 ± 0.2 and 28.2 ± 0.2 degrees two-theta. The most characteristic peaks of Form IV are at about 11.9 ± 0. 2, 14.2 ± 0.2, 18.3 ± 0.2, 19.2 ± 0.2, 21.7 ± 0.2, and 24.2 ± 0.2 degrees two-theta.

The characteristic peaks of Form V are described at page 16, lines 12-15, of WO 02/00216:

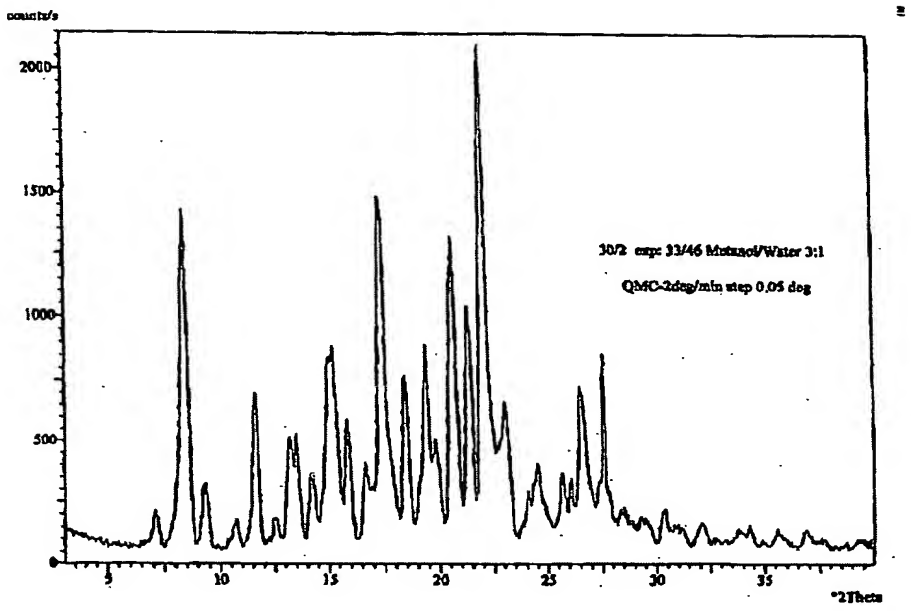
> Carvedilol Form V ("Form V") is characterized by an X-ray diffraction pattern with peaks at about 4.1 ± 0. 2, 10.3 ± 0.2, 10.7 ± 0.2, 11.5 ± 0.2, 12.6 ± 0.2, 14.0 ± 0.2, 14.8 ± 0.2, 15.4 ± 0.2, 16.4 ± 0.2, 16.8 ± 0.2, 18.8 ± 0.2, 20.8 ± 0.2, 21.1 ± 0.2, 21.6 ± 0.2, and 25.4 ± 0.2, degrees two-theta.

These PXRD peaks differ from the peaks that characterize Form VI. See the present application, at page 4, lines 10-13:

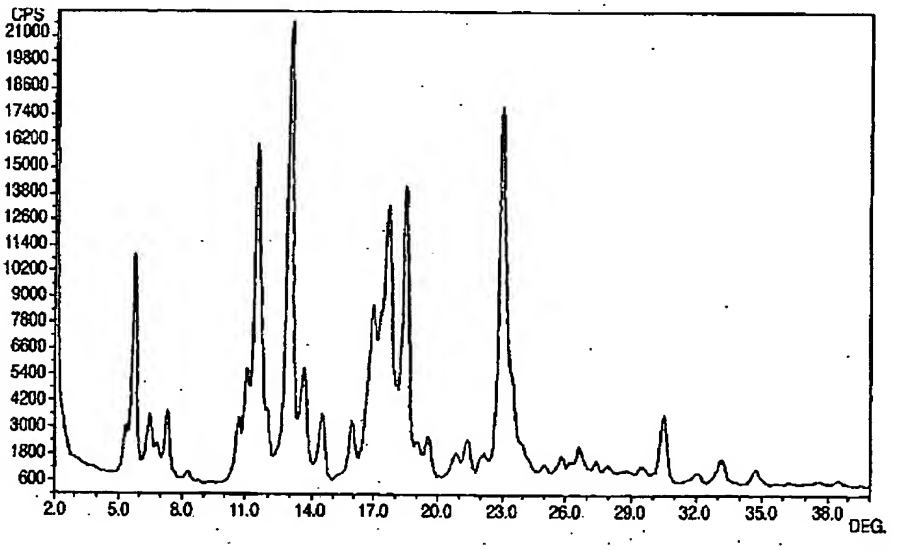
> Carvedilol solvate Form VI is characterized by a PXRD pattern (FIG. 1) with peaks at about 6.5, 7.3, 16.0, and 30.5±0.2 degrees two-theta. Further PXRD peaks were observed at about 5.8, 10.7, 11.1, 11.5, 13.1, 13.7, 16.8, 17.7, 18.5, and 23.0±0.2 degrees two-theta.

Furthermore, a comparison of the overall PXRD patterns of Forms III, IV, and V with that of Form VI indicates that Forms III, IV, and V are not the same as Form VI.

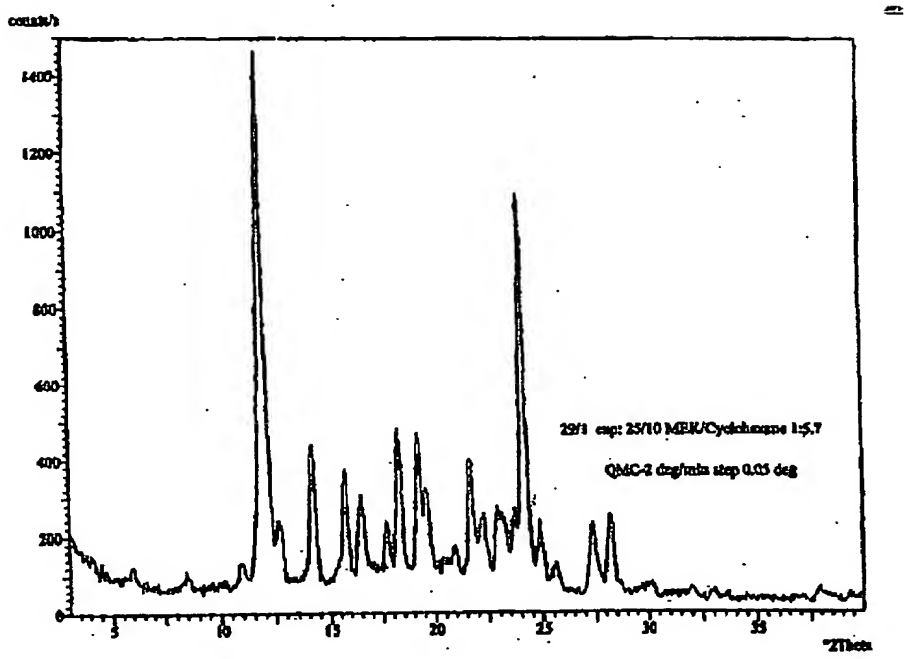
Form III (Figure 1 from WO 02/00216)



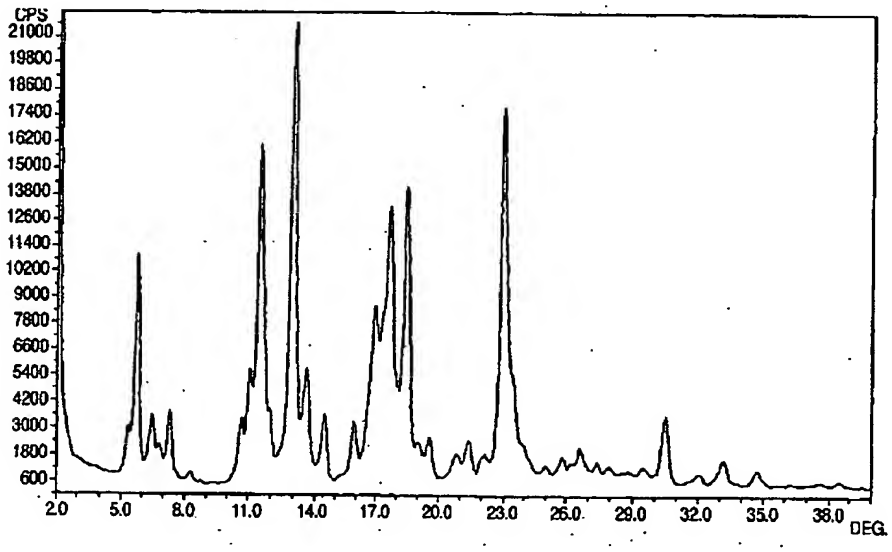
Form VI (Figure 1 of the present application)



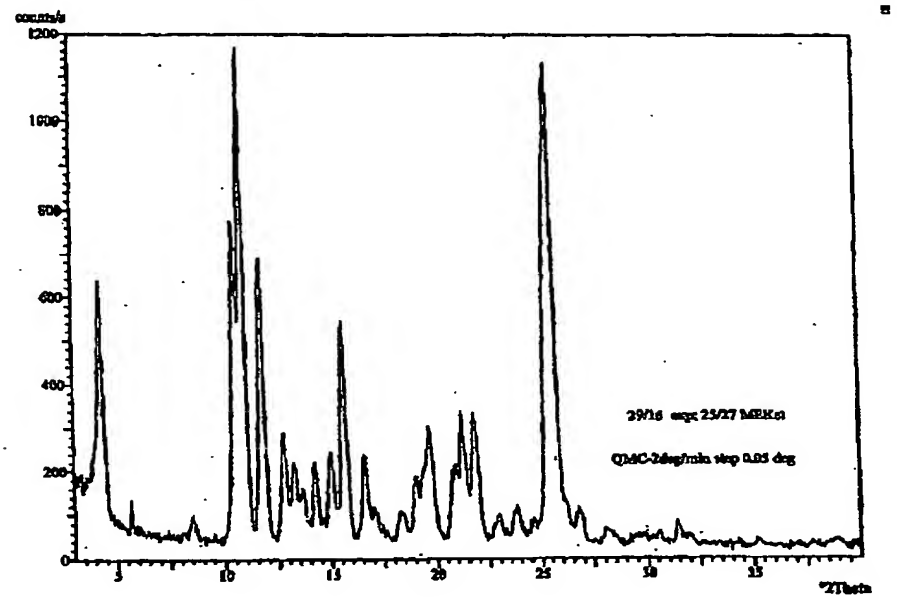
Form IV (Figure 3 from WO 02/00216)



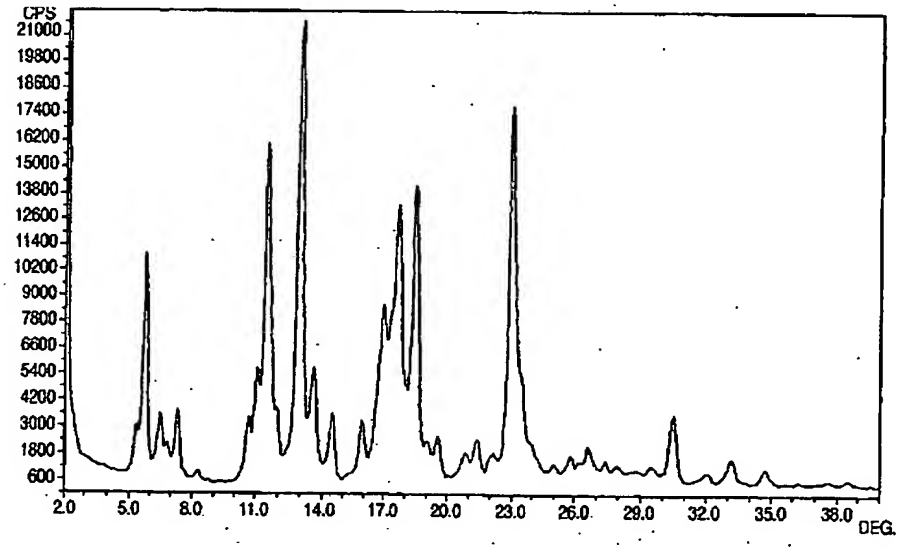
Form VI (Figure 1 of the present application)



Form V (Figure 5 from WO 02/00216)



Form VI (Figure 1 of the present application)



Given these differences in PXRD patterns, it must be concluded that none of Forms III, IV, or V is the same crystalline form as Form VI.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 18 and 19 were rejected as being anticipated under 35 U.S.C. §102(e) by US Patent Application Publication US 2004/152756.

US Patent Application Publication US 2004/152756 discloses a purportedly new crystalline form of carvedilol referred to as Form III.

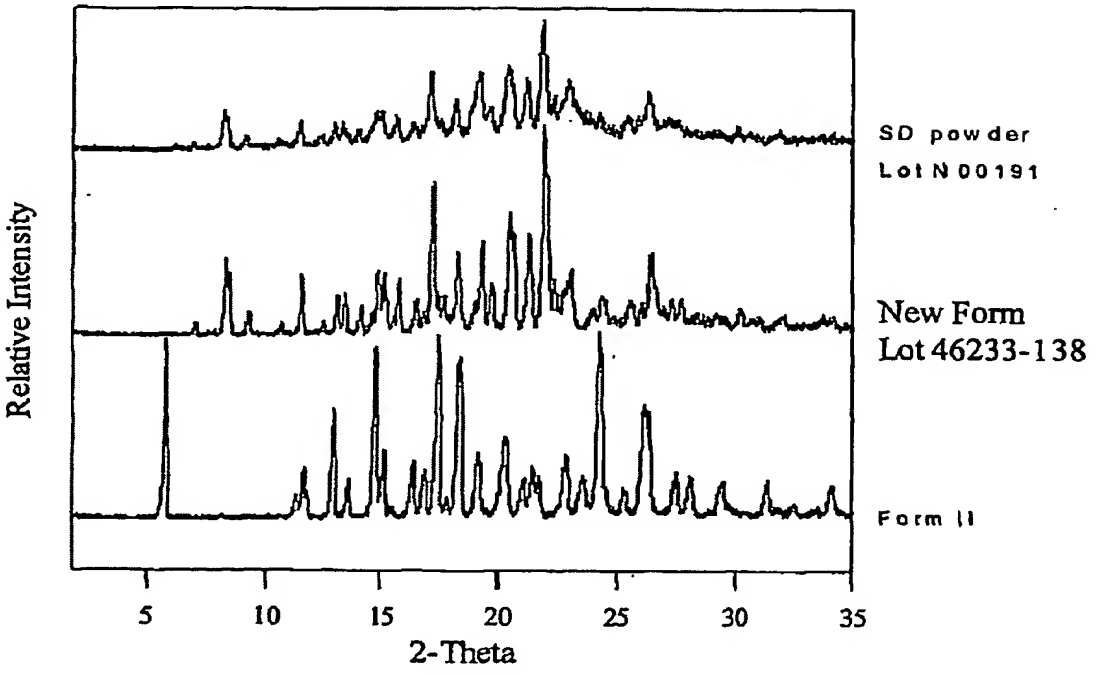
Form III is a different crystalline form as compared to Form VI because Form III has a different PXRD pattern from Form VI. The characteristic peaks of Form III are listed at paragraph [0046]: "Carvedilol Form III has an X-ray powder diffraction pattern which comprises characteristic peaks at about 8.4, 17.4 and 22.0 degrees two-theta."

These PXRD peaks differ from the peaks that characterize Form VI. See the present application, at page 4, lines 10-13:

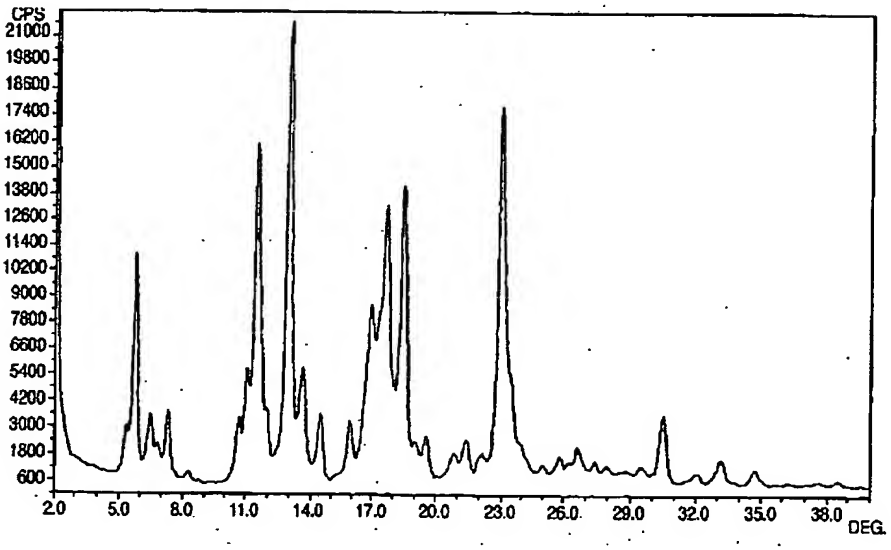
> Carvedilol solvate Form VI is characterized by a PXRD pattern (FIG. 1) with peaks at about 6.5, 7.3, 16.0, and 30.5±0.2 degrees two-theta. Further PXRD peaks were observed at about 5.8, 10.7, 11.1, 11.5, 13.1, 13.7, 16.8, 17.7, 18.5, and 23.0±0.2 degrees two-theta.

Furthermore, a comparison of the overall PXRD pattern of Form III with that of Form VI indicates that Form III is not the same as Form VI.

Form III (middle trace in Figure 9 from US 2004/0152756)



Form VI (Figure 1 of the present application)



Given these differences in PXRD patterns, it must be concluded that Form III is not the same crystalline form as Form VI.

Accordingly, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §103

Claims 1-10 and 17 were rejected as being obvious over Chen et al., 1998, Chinese J. Struct. Chem. 17:325-328 (Chen).

The difference between Chen's crystalline form and the claimed Form VI is that Chen's form and the claimed Form VI are different crystalline forms with different physical characteristics such as X-ray diffraction patterns (see the Office Action, page 14, lines 1-3). The Office Action states that one would be motivated to make the claimed Form VI because of the expectation that Form VI would have enhanced properties compared to Chen's form. See the Office Action, page 15, lines 11-14: "One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc." and lines 17-21: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc." *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) were cited as supporting this rejection.

The Applicants traverse this rejection. It is respectfully submitted that this obviousness rejection relies on hindsight based on the Applicants' disclosure that the claimed crystalline Form VI exists. Before the Applicants' invention, Form VI was an unknown substance. Moreover, there were no known ways of making Form VI. That some other crystalline form such as that disclosed in Chen might have existed does not make obvious the particular claimed crystalline Form VI since there could have been no motivation to produce Form VI when Form VI was not known to exist. Also, there could have been no reasonable expectation of successfully producing Form VI when there was no known way of making Form VI. Furthermore, the most pertinent case law supports a conclusion that the presently claimed Form VI is non-obvious.

This rejection is based on the premise that motivation to make the present invention could be found in the knowledge of the existence of Chen's form and the possibility that

other crystalline forms of carvedilol might exist and might have similar properties to that of Chen's crystalline form. Such "motivation," even if it existed, is not specific enough to provide the motivation necessary to sustain an obviousness rejection of the present claims. This motivation is not specific to Form VI. It represents a general incentive to look for additional crystalline forms, once it is known that crystalline forms of a compound exist. But this is not sufficient motivation to sustain an obviousness rejection. "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559, 34 U.S.P.Q. 2d 1210, 1216 (Fed. Cir. 1995).

The present claims are directed to specific subject matter – a particular crystalline form of carvedilol. At most, the existence of other crystalline forms of carvedilol in the prior art could have provided a general suggestion to explore the possibility that there may be additional carvedilol crystalline forms in addition to those already known. As explained below, the Court of Appeals for the Federal Circuit has held that such general motivation to explore a new area is insufficient to sustain an obviousness rejection. Moreover, decisions of various tribunals in connection with the obviousness of crystalline forms have repeatedly found that such general motivation is inadequate.

In order to arrive at the presently claimed crystalline form, based merely on the general motivation provided by the existence of other crystalline forms, one skilled in the art would have had to vary a large number of parameters in an attempt to find the right parameters for producing the claimed crystalline form. Among such parameters would be: solvent or solvent systems, temperature, time of reaction, and carvedilol starting material (i.e., type of crystalline form or amorphous form). All of these parameters would have to be varied independently, without any specific guidance from the prior art. It can readily be seen that the number of permutations of these parameters would be enormous, with no guidance to narrow down the possibilities.

In view of the lack of specific guidance in the prior art, and the large number of parameters to be varied, the argument provided in the Office Action at most demonstrates that it might have been "obvious to try" to make the claimed invention. The argument in the Office Actions thus falls into the type of obvious-to-try error cautioned against by the Federal Circuit in *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988):

> The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Furthermore, given the total lack of guidance in the prior art as to the specific reaction parameters that would have led to the claimed crystalline form, the argument provided in the Office Action demonstrates at most that those skilled in the art would have been motivated to explore a promising field of experimentation. Thus, the argument in the Office Action also falls into the second type of error cautioned against by the Federal Circuit in *O'Farrell*:

> In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

853 F.2d at 903, 7 USPQ2d at 1681.

See also *Ex parte Obukowicz*, 27 USPQ 2d 1063, 1065 (Bd. Pat. App. & Int. 1992):

> At best, the [cited reference] is but an invitation to scientists to explore a new technology that seems a promising field of experimentation. The [cited reference] is of the type that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it. Such a suggestion may make an approach "obvious to try" but it does not make the invention obvious.

Case law in which the obviousness of crystalline forms was at issue supports the Applicants' position. In *In re Certain Crystalline Cefadroxil Monohydrate*, 15 USPQ2d 1263 (U.S. Intern. Trade Comm. 1990), the U.S. International Trade Commission (ITC) reversed a finding of one of its administrative law judges (ALJs) that a Bristol-Myers patent

claiming a particular crystalline form of cefadroxil was obvious over two prior art patents that disclosed processes for producing various forms of cefadroxil.

Using reasoning similar to that of the current Office Action, the ALJ based her conclusion of obviousness on a determination that there was a general motivation to find other crystalline forms of cefadroxil and that the claimed crystalline form could have been obtained by methods that were obvious to those of ordinary skill in the art. The ITC summarized the ALJ's reasoning as follows:

> [T]he ID[4] concluded that if these prior art methods were modified in a certain manner, using changes obvious to those with ordinary skill in the art, the Bouzard monohydrate[5] would be produced.
>
> In effect, the ALJ concluded that because there was motivation to make a commercially usable form of cefadroxil, and obvious changes to the processes described in the prior art would result in production of the Bouzard monohydrate, which has been commercially successful, the Bouzard monohydrate was obvious under 35 U.S.C. §103. We do not believe that either the ID's inquiries or its conclusions comport with controlling law. The ID's method of analysis is, in fact, identical to that found in the TEO ID, which the Federal Circuit[6] rejected as:
>
> > irrelevant to whether the Bouzard discovery would have been obvious in terms of §103. The question before the Commission was not whether the Bouzard crystal form could have been duplicated with experimentation or with even minor chemical process changes; the question was whether this new crystal form, as a composition of

[4] "ID" refers to "initial determination," the name given to the ALJ's report.

[5] The Bouzard monohydrate was the crystalline form of cefadroxil claimed in the Bristol-Myers patent at issue.

[6] In prior proceedings concerning this dispute, the ITC had denied Bristol-Myers temporary relief (a "TEO") because the ITC concluded that the Bristol-Myers patent was likely to be found invalid for obviousness over the two prior art patents. The Federal Circuit reversed this decision on temporary relief, finding that the Bristol-Myers patent would likely be found non-obvious over the two patents. This Federal Circuit decision was reported at Bristol-Myers Co. v. U.S. International Trade Commission, 15 USPQ2d 1258 (Fed. Cir. 1989) as a non-precedential decision. Thus, this Federal Circuit decision is not binding precedent, although the Applicants believe the reasoning therein is persuasive and would likely be followed again, were the Federal Circuit faced with similar facts.

> matter, would have been obvious from the teachings of the prior art.
>
> . . .
>
> It is insufficient that the prior art shows methods that some (but not all) chemists were able to modify, to produce the Bouzard crystalline form. There must be a suggestion in the prior art that the Bouzard crystal structure would or should be made, whether by manipulation of the Garbrecht or Crast II[7] processes, or by any other process. In factual and legal point is In re Cofer, 354 F.2d 664, 668, 148 USPQ 268, 271 (CCPA 1966), wherein the court held that a new crystalline form of a compound would not have been obvious absent evidence that "the prior art suggests the particular structure or form of the compound or composition as well as suitable methods for obtaining that structure or form."

15 USPQ2d at 1268 [footnotes omitted, emphasis added]

The ITC went on to find the Bristol-Myers patent non-obvious, stressing that the motivation in the prior art was too general, i.e., not directed to the particular claimed crystalline form and that the particular claimed crystalline form was unpredictable:

> The ID merely determined that motivation existed to produce an improved form of cefadroxil - not the particular structure represented by the Bouzard monohydrate. ... The ID further found that:
>
> > the form of cefadroxil could not be predicted accurately until the experiment was made. Dr. Garbrecht expected that the cefadroxil DMF solvate produced by his '282 patent process would be crystalline, and that the final product of the aqueous crystallization procedure would be a solid, but he had no expectations about the nature of its crystallinity or hydration. (Tr. 342-44.) Dr. Baldwin [a Bristol expert witness] agreed with Dr. Garbrecht, and testified that no chemist could predict the form of hydration that a cefadroxil

[7] Garbrecht and Crast II were the two prior art patents.

crystal could take. (Tr. 228.)

Respondents have not disputed or contested this finding. To the contrary, one of their own expert witnesses also testified that he would not have been able to predict in advance the form of the Bouzard monohydrate.

Consequently, the record indicates that the prior art did not and could not have suggested the particular structure and form of the Bouzard monohydrate. Respondents argue that the "predictability" of the Bouzard monohydrate has no relevance to a determination on obviousness, and instead direct our attention to the evidence that they submitted and the ID discussed concerning the obviousness of the modifications to the Crast and Garbrecht patents needed to produce the Bouzard monohydrate. The Federal Circuit, however, has ruled that "predictability" does matter, and that respondents' reliance on the obviousness of changes to prior art processes is in vain ...

15 USPQ2d at 1269-1270 [footnotes omitted]

The facts in the present application are similar to those of *In re Certain Crystalline Cefadroxil Monohydrate.* The presently claimed crystalline form was unknown and its structure was thus unpredictable before the Applicants' invention. The motivation cited by the Office Action in the present application, like the motivation in *In re Certain Crystalline Cefadroxil Monohydrate,* is merely general, not directed to the particular claimed crystalline form. Since the Office Action provided no evidence that the prior art contained disclosures of processes that could be used to make Form VI, the Office Action must be relying on the obviousness of changes to prior art processes, such as those used to make Chen's form. The losing party in *In re Certain Crystalline Cefadroxil Monohydrate* similarly relied on changes to prior art processes. These similarities between the present rejection and *In re Certain Crystalline Cefadroxil Monohydrate* should lead to the same conclusion as in *In re Certain Crystalline Cefadroxil Monohydrate* – the presently claimed crystalline Form VI is non-obvious.

Although cited in the Office Action, *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) support the Applicants' position. In *Cofer*, the Board of Appeals (quoting *Hartop*)

had sustained a rejection for obviousness of a new crystal form of a compound, stating:

> [M]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable ...

354 F.2d at 667, 148 USPQ at 271.

The Court of Customs and Patent Appeals ruled that the broad proposition embodied in the Board's statement was not sound. The Court stated:

> The cited cases fail to support the broad proposition that:
> . . . merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable.

354 F.2d at 667, 148 USPQ at 271.

The Court went on to state that the factors to be given weight in determining whether the claimed crystalline form was obvious were whether the particular claimed crystalline structure was suggested by the prior art and whether the prior art provided methods of obtaining that particular structure.

> We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. [emphasis added]

354 F.2d at 668, 148 USPQ at 272.

Since neither the particular claimed structure, nor methods of obtaining that structure, were disclosed in the art, the Court reversed the rejection for obviousness.

Applying the reasoning of *Cofer* to the present claims leads to a conclusion of non-obviousness since the prior art suggests neither the particular structure of the presently claimed crystalline Form VI nor methods of obtaining the claimed crystalline Form VI.

Other case law supports a finding of non-obviousness for the present claims. In *In re Irani*, 427 F.2d 806, 166 USPQ 24 (CCPA 1970), the Court of Customs and Patent Appeals again reversed the Board of Patent Appeals after the Board held obvious claims to a crystalline form of a compound based on a disclosure of a non-crystalline form of the same compound. The Court found that the prior art did not suggest that the particular claimed crystalline compound existed or provide a method for making it.

> Upon due consideration of all these reference disclosures concerning the physical forms in which various known aminophosphonic acids exist, we think the most definite conclusion that can be reached is that some of these acids can be obtained in crystalline form and some cannot, and that of the former group some can be obtained with ease by conventional procedures and some only with great difficulty by specially devised techniques. This being the case, we cannot conclude that it would have been obvious that crystalline, anhydrous ATMP could exist.
>
> As stated above, even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline anhydrous ATMP could be produced, we are not convinced by this record that it would also have been obvious *how* this could be achieved. We note that neither the examiner nor the board has contended that a suitable process would have been obvious. [italics in original]

427 F.2d at 809, 166 USPQ at 27.

The present situation is similar to that in *Cofer* and *Irani*. The prior art fails to suggest the existence of the particular claimed crystalline form and the prior art fails to suggest methods by which that particular crystalline form can be obtained. Given the holdings in *Cofer* and *Irani*, it is clear that the present claims, like those in *Cofer* and *Irani*, are not obvious.

The lack of disclosure of a method of making the claimed crystalline Form VI in the prior art leads to a conclusion of non-obviousness for the present claims not only under *Cofer* and *Irani* but also under *In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979). In *Grose*,

the court made it clear that a conclusion of obviousness of one compound based upon its structural similarity to another compound depends upon the assumption that the method disclosed for producing the prior art compound can be used to produce the new compound.

> One of the assumptions underlying a prima facie obviousness rejection based upon a structural relationship between compounds, such as adjacent homologs, is that a method disclosed for producing one would provide those skilled in the art with a method for producing the other.
>
> 592 F.2d at 1168, 201 USPQ at 63.
>
> Failure of the prior art to disclose or render obvious a method for making any composition of matter ... precludes a conclusion that the composition would have been obvious.
>
> 592 F.2d at 1168, 201 USPQ at 64.

There is no evidence of record that shows that the presently claimed crystalline Form VI can be produced by the methods disclosed in the prior art. Given that the production of particular crystalline forms is highly sensitive to the precise reaction conditions used, it is highly likely that the prior art methods could not produce the presently claimed crystalline form. The prior art is devoid of any suggestion as to the particular modifications of prior art processes that would lead to the production of the particular claimed crystalline Form VI. Accordingly, the presently claimed crystalline Form VI is non-obvious under *Grose*.

Another case holding that the disclosure of one crystalline form of a pharmaceutical compound does not make obvious other, different forms is *Ex parte Gala*, 2002 WL 851814 ((Board of Patent Appeals & Interferences, date unavailable).[8] In *Ex parte Gala*, the Board reversed a rejection for obviousness of claims directed to a particular crystalline form of a pharmaceutical compound, Form 2 of loratadine. The cited art included a patent (Villani) that disclosed a different crystalline form of loratadine, Form I.

> Villani discloses polymorph form 1 of loratadine, but does not disclose or suggest that loratadine may assume distinct, crystalline polymorphic forms having different

[8] A copy of this decision is provided herewith as Exhibit A.

> physical properties. Nor does Villani teach a person having ordinary skill in the art how to make polymorph form 2 of loratadine.
>
> *Ex parte Gala*, page 2.

The Examiner in *Gala*, like the Examiner in the present Office Action, had relied on *Hartop*, stating: "[M]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable." (*Ex parte Gala*, page 3). The Board summarized the Examiner's reasoning as follows:

> According to the examiner, polymorph form 2 loratadine is merely another form of an old product (polymorph form 1 loratadine) and both forms possess the same utility. Accordingly, the examiner concludes that applicants' claims, reciting polymorph form 2 loratadine, are unpatentable.
>
> *Ex parte Gala*, page 3.

The Board rejected this reasoning and reversed the rejection, stating that *Cofer* "substantially discredited" this reasoning.

The current rejection is inconsistent with well-established principles relating to the issue of obviousness of chemical compounds. It is well settled that the properties of a claimed chemical compound must be taken into account when conducting an obviousness inquiry. See, e.g., *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963): "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." The *Grose* court reiterated this principle and stated that differences in X-ray diffraction patterns between a claimed compound and prior art compounds were among the types of differences in properties that support a conclusion of non-obviousness for claimed compounds.

> Determining whether a chemical composition is prima facie obvious from another may rest on whether differences in structure and properties of the compositions can be accounted for by obvious modifications in the synthesis process or by obvious modifications of one composition to yield the other. If the differences in X-ray diffraction data between the zeolites here involved had indicated an actual difference in crystal structure, the present record would

belie a conclusion that such differences resulted from obvious modifications of any prior art synthesis process or from obvious modifications of Milton's zeolite R to yield the claimed zeolite.

592 F.2d at 1168, 201 USPQ at 63.

The X-ray diffraction pattern of the presently claimed crystalline Form VI differs from the X-ray diffraction patterns disclosed in the prior art. These differences represent real, significant differences in structure, and thus properties, between Form VI and prior art forms. "Because of differences in the dimensions, shape, symmetry, capacity (number of molecules), and void volumes of their unit cells, the different polymorphs of a given substance have different physical properties arising from differences in molecular packing." David J. W. Grant, *Theory and Origin of Polymorphism,* in Drugs of the Pharmaceutical Sciences, vol. 95, Polymorphism in Pharmaceutical Solids, Chapter 1, sentence connecting pages 5 to 8 (Harry G. Brittain ed., 1999).[9] Physical properties that may differ among various polymorphs include: packing properties, thermodynamic properties, spectroscopic properties, kinetic properties, surface properties, and mechanical properties. *Id.* at 7. Because different crystalline forms exhibit different structure and different properties, the disclosure of one crystalline form does not render obvious another crystalline form. The different structures and different properties of crystalline forms make this art unpredictable. There is a large amount of uncertainty involved in arriving at any particular crystalline form, or even knowing that such a form exists. The process of making new crystalline forms is essentially a process of trial and error. See, e.g., Rouhi, at p. 32: "But no method yet exists to predict the polymorphs of a solid compound with significant certainty. The search for polymorphs is largely an empirical exercise." The Patent Office has recognized this unpredictability by routinely granting patents for novel crystalline forms over both the free form and other known crystalline forms.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1-10 and 17 were rejected as being obvious over U.S. Patent No. 4,503,067.

[9] A copy of Grant is enclosed herewith as Exhibit B.

This rejection, like the rejection over Chen discussed above, is based on the disclosure of a crystalline form of carvedilol that is different from the presently claimed Form VI. As in the rejection over Chen, here the Office Action states that one would be motivated to make the claimed Form VI because of the expectation that Form VI would have enhanced properties compared to that of the form of U.S. Patent No. 4,503,067 (see the Office Action, page 18, lines 9-12: "One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc." and lines 15-19: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc."). *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) were cited as supporting this rejection.

The Applicants traverse this rejection. This rejection is essentially the same as the rejection over Chen discussed above in that it is based on the proposition that the disclosure of a crystalline form of carvedilol different from the claimed Form VI makes obvious the present claims directed to Form VI. Such a proposition suffers from the same lack of specificity with respect to motivation and lack of known methods to make Form VI as the rejection over Chen. As for the rejection over Chen, the prior art does not teach which particular combination of solvents, time, temperature, etc. should be chosen from among the vast number of possible combinations of such parameters in order to produce Form VI. Again, the prior art did not even contain any disclosure or suggestion that Form VI exists.

As for the rejection over Chen, the case law discussed above (*Deuel*, *O'Farrell*, *Obukowicz*, *In re Certain Crystalline Cefadroxil Monohydrate*, *Cofer*, *Hartop*, *Irani*, *Gala*, *Grose*, *Papesch*), for the same reasons as discussed above, leads to the conclusion that this rejection is also in error.

Thus, for the same reasons that were discussed above in connection with the rejection over Chen, the Applicants respectfully request that this rejection be withdrawn.

Claims 1-10 and 17 were rejected as being obvious over European Patent Application EP 0918055.

This rejection, like the rejection over Chen discussed above, is based on the disclosure of crystalline forms of carvedilol that are different from the presently claimed Form VI. As in the rejection over Chen, here Office Action states that one would be motivated to make the claimed Form VI because of the expectation that Form VI would have enhanced properties compared to that of the forms of European Patent Application EP 0918055 (see the Office Action, page 21, lines 7-10: "One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc." and lines 13-17: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc."). *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) were cited as supporting this rejection.

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As for the rejection over Chen, the case law discussed above (*Deuel*, *O'Farrell*, *Obukowicz*, *In re Certain Crystalline Cefadroxil Monohydrate*, *Cofer*, *Hartop*, *Irani*, *Gala*, *Grose*, *Papesch*), for the same reasons as discussed above, leads to the conclusion that this rejection is also in error.

Thus, for the same reasons that were discussed above in connection with the rejection over Chen, the Applicants respectfully request that this rejection be withdrawn.

Claims 1-10 and 17 were rejected as being obvious over European Patent Application EP 0893440.

This rejection, like the rejection over Chen discussed above, is based on the disclosure of crystalline forms of carvedilol that are different from the presently claimed Form VI. As in the rejection over Chen, here Office Action states that one would be motivated to make the claimed Form VI because of the expectation that Form VI would have enhanced properties compared to that of the forms of European Patent Application EP 0893440 (see the Office Action, page 24, lines 5-8: "One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc." and lines 11-15: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc."). *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) were cited as supporting this rejection.

The Applicants traverse this rejection. This rejection is essentially the same as the rejection over Chen discussed above in that it is based on the proposition that the disclosure of a crystalline form of carvedilol different from the claimed Form VI makes obvious the present claims directed to Form VI. Such a proposition suffers from the same lack of specificity with respect to motivation and lack of known methods to make Form VI as the rejection over Chen. As for the rejection over Chen, the prior art does not teach which particular combination of solvents, time, temperature, etc. should be chosen from among the vast number of possible combinations of such parameters in order to produce Form VI. Again, the prior art did not even contain any disclosure or suggestion that Form VI exists.

As for the rejection over Chen, the case law discussed above (*Deuel*, *O'Farrell*, *Obukowicz*, *In re Certain Crystalline Cefadroxil Monohydrate*, *Cofer*, *Hartop*, *Irani*, *Gala*, *Grose*, *Papesch*), for the same reasons as discussed above, leads to the conclusion that this rejection is also in error.

Thus, for the same reasons that were discussed above in connection with the rejection over Chen, the Applicants respectfully request that this rejection be withdrawn.

Claims 1-10 and 17 were rejected as being obvious over International Patent Publication WO 99/05105.

This rejection, like the rejection over Chen discussed above, is based on the disclosure of crystalline forms of carvedilol that are different from the presently claimed Form VI. As in the rejection over Chen, here Office Action states that one would be motivated to make the claimed Form VI because of the expectation that Form VI would have enhanced properties compared to that of the forms of International Patent Publication WO 99/05105 (see the Office Action, page 27, lines 1-4: "One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc." and lines 7-11: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc."). *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) were cited as supporting this rejection.

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As for the rejection over Chen, the case law discussed above (*Deuel*, *O'Farrell*, *Obukowicz*, *In re Certain Crystalline Cefadroxil Monohydrate*, *Cofer*, *Hartop*, *Irani*, *Gala*,

Grose, *Papesch*), for the same reasons as discussed above, leads to the conclusion that this rejection is also in error.

Thus, for the same reasons that were discussed above in connection with the rejection over Chen, the Applicants respectfully request that this rejection be withdrawn.

Claims 1-10 and 17 were rejected as being obvious over International Patent Publication WO 02/00216.

This rejection, like the rejection over Chen discussed above, is based on the disclosure of crystalline forms of carvedilol that are different from the presently claimed Form VI. As in the rejection over Chen, here Office Action states that one would be motivated to make the claimed Form VI because of the expectation that Form VI would have enhanced properties compared to that of the forms of International Patent Publication WO 02/00216 (see the Office Action, page 29, line 22, to page 30, line 3: "One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc." and page 30, lines 6-10: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc."). *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) were cited as supporting this rejection.

The Applicants traverse this rejection. This rejection is essentially the same as the rejection over Chen discussed above in that it is based on the proposition that the disclosure of a crystalline form of carvedilol different from the claimed Form VI makes obvious the present claims directed to Form VI. Such a proposition suffers from the same lack of specificity with respect to motivation and lack of known methods to make Form VI as the rejection over Chen. As for the rejection over Chen, the prior art does not teach which particular combination of solvents, time, temperature, etc. should be chosen from among the vast number of possible combinations of such parameters in order to produce Form VI. Again, the prior art did not even contain any disclosure or suggestion that Form VI exists.

As for the rejection over Chen, the case law discussed above (*Deuel*, *O'Farrell*, *Obukowicz*, *In re Certain Crystalline Cefadroxil Monohydrate*, *Cofer*, *Hartop*, *Irani*, *Gala*, *Grose*, *Papesch*), for the same reasons as discussed above, leads to the conclusion that this rejection is also in error.

Thus, for the same reasons that were discussed above in connection with the rejection over Chen, the Applicants respectfully request that this rejection be withdrawn.

Claims 1-10 and 17 were rejected as being obvious over U.S. Patent Application Publication US 2004/0152756.

This rejection, like the rejection over Chen discussed above, is based on the disclosure of crystalline forms of carvedilol that are different from the presently claimed Form VI. As in the rejection over Chen, here Office Action states that one would be motivated to make the claimed Form VI because of the expectation that Form VI would have enhanced properties compared to that of the forms of U.S. Patent Application Publication US 2004/0152756 (see the Office Action, page 32, lines 19-22: "One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc." and page 33, lines 3-7: "One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc."). *In re Cofer*, 354 F.2d 664, 148 U.S.P.Q. 268 (CCPA 1966) and *Ex parte Hartop*, 139 U.S.P.Q. 525 (Bd. Pat. Appeals 1962) were cited as supporting this rejection.

The Applicants traverse this rejection. This rejection is essentially the same as the rejection over Chen discussed above in that it is based on the proposition that the disclosure of a crystalline form of carvedilol different from the claimed Form VI makes obvious the present claims directed to Form VI. Such a proposition suffers from the same lack of specificity with respect to motivation and lack of known methods to make Form VI as the rejection over Chen. As for the rejection over Chen, the prior art does not teach which particular combination of solvents, time, temperature, etc. should be chosen from among the

vast number of possible combinations of such parameters in order to produce Form VI. Again, the prior art did not even contain any disclosure or suggestion that Form VI exists.

As for the rejection over Chen, the case law discussed above (*Deuel*, *O'Farrell*, *Obukowicz*, *In re Certain Crystalline Cefadroxil Monohydrate*, *Cofer*, *Hartop*, *Irani*, *Gala*, *Grose*, *Papesch*), for the same reasons as discussed above, leads to the conclusion that this rejection is also in error.

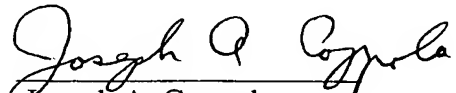
Thus, for the same reasons that were discussed above in connection with the rejection over Chen, the Applicants respectfully request that this rejection be withdrawn.

The time for responding to the Office Action was set for December 1, 2006. Therefore, it is believed that this response is timely. If this is in error, please treat this response as containing a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this paper and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

Date: March 1, 2007

BY: 

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